COMMENTARY

The report of the New England Regional Infant Cardiac Program (NERICP) was a landmark publication when it appeared as a lengthy supplement to *Pediatrics* in 1980. For the first time, a region had cooperatively and critically analyzed the care it was delivering to seriously ill infants with heart disease. As such it became a model for subsequent attempts to assess all aspects of care delivery, not only for those with heart disease but for other diseases as well. This is particularly important at present, given the concerns that have been raised about outcome data, costs, access, and long-term results.

When one reviews this supplement in 1998, the breadth of the study still appears most impressive. There was attention focused on such items as case finding, transportation to a cardiovascular center, communications between community physicians and the centers, cost of diagnostic and surgical procedures, education of parents, psychosocial elements, and outcome. All these items that were addressed in the 1970s assume even more importance as we approach the 21st century.

The NERICP also served as the model from which other regional programs that focused on infants with cardiac disease could be studied and led to the Baltimore-Washington and the Midwestern pediatric cardiac programs.

The report provided a wealth of epidemiologic data that have been extremely useful when current programs are analyzed. Mortality rates declined with fewer infants dying before being evaluated at a regional center. An increased awareness on the part of community physicians of the possibility of the existence of a cardiac problem was notable as evidenced by more sick newborn infants being admitted to regional centers for diagnostic evaluation and management.

The report covers a period of time when interventional procedures and early surgical repair of certain lesions were just beginning to be undertaken. For example, this was before arterial switch operations for transposition of the great arteries, balloon valvuloplasty for critical pulmonary valve stenosis, and the Norwood procedure for the hypoplasic left heart syndrome. Nevertheless, each center was able to review its results and compare them with other centers in the region. This interchange led overall to improved survival statistics and, in some instances, discontinuing surgical management at some of the centers.

Today, and for the future, each regional cardiovascular center must closely evaluate its total operation in terms of patient volume, short-term and long-term outcome data, costs and case findings, communication, and parent patient education as was done in the NERICP. Although access to a center should be facilitated, the number of regional centers per population base has to be critically assessed by impartial consultants. This approach is a necessity given the current emphasis on access to specialized care, cost containment, and results. Although extremely important, currently there is a strong likelihood that this will assume even more importance in the future as well. Thus, this initial report of the NERICP has served admirably as the template for what now must take place in all regions of the country. It was ahead of its time but fortunately has stood the test of time and, therefore, is deemed a worthy contribution to the exciting history of pediatric cardiovascular disease in the United States.

**ABSTRACT OF ORIGINAL ARTICLE (STARKO ET AL)**. During an outbreak of influenza A, seven patients with Reye’s syndrome and 16 ill classmate control subjects were evaluated for characteristics of the patients’ prodromal illness and the control subjects’ illness and for medication usage. Patients during the prodrome and control subjects had similar rates of sore throat, cough, headache, and gastrointestinal complaints except for documented fever which occurred significantly more often in patients than in control subjects (P = .05). While medications which did not contain salicylate were taken as frequently by patients as control subjects, patients took more salicylate-containing medications than did control children (P < .01). All seven patients took salicylate whereas only eight of 16 control subjects did so.

**SUPPLEMENT**

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(P < .05). Patients took larger doses of salicylate than did the entire control group (P < .01). When the eight control subjects who took salicylate were compared with the patients, the patients still tended to take larger doses (P = .08). Patients with fever took salicylate more frequently than control subjects with fever (P < .01). In addition, salicylate consumption was correlated with severity of Reye’s syndrome (P < .05). It is postulated that salicylate, operating in a dose-dependent manner, possibly potentiates by fever, represents a primary causative agent of Reye’s syndrome.

ABSTRACT OF ORIGINAL ARTICLE (ARROWSMITH ET AL.). The number of cases of Reye syndrome reported annually to the Centers for Disease Control and Prevention declined markedly between 1980 and 1985. In this article we present pharmaceutical marketing research data that suggest sharp decreases in the use and purchase of children’s aspirin between 1980 and 1985. These trends appear to correspond to the decrease in reporting of Reye syndrome cases. Additionally, analysis of physician mentions of aspirin and acetaminophen for treating flu and chickenpox showed statistically significant trends toward increasing recommendations for use of acetaminophen. Trends in wholesale purchases of aspirin and acetaminophen by drug stores from 1979 through 1985 demonstrated a significant decline for the 81-mg children’s aspirin tablet and an increase in purchases of children’s acetaminophen products. Many factors may influence physician and parents’ choice of analgesic/antipyretic medication, including information about Reye syndrome. Data suggest that a continuing decline in the use of aspirin for children may be accompanied by a continuing decline in the reported number of Reye syndrome cases.

In 1963, Reye and colleagues first described a distinct clinical and pathologic syndrome of encephalopathy and characteristic fatty degeneration of the liver after a viral-like prodromal illness. During the ensuing years, the etiology of this sometimes lethal syndrome remained a mystery, although multiple putative contributory causative factors were proposed, including viral infections, aflatoxin, pesticides, and various medications. For reasons that remain poorly understood, an increase in reporting of Reye’s syndrome cases occurred during the late 1970s and early 1980s. More than 650 cases were reported to the Centers for Disease Control and Prevention (CDC) in 1977 to 1978.

The articles by Starko et al and Arrowsmith et al included among the historic articles reviewed in this issue of Pediatrics anchor two interconnected aspects of the Reye’s syndrome and aspirin story. This is a story that unfolded over an entire decade, culminating in a dramatic decline in incidence of Reye’s syndrome coincident with a major and permanent change in physician prescribing and consumer use of aspirin in children.

A cluster of Reye’s syndrome cases occurred in Arizona school children in 1978 during an outbreak of influenza A/Brazil illness. During this epidemic, Dr Karen Starko, then a young Public Health Service Officer, and her colleagues conducted a retrospective case-control study of seven children, 8 to 15 years of age, who were hospitalized with the diagnosis of Reye’s syndrome between December 21 and 25, 1978. The purpose of Starko’s study was to assess the possible contribution of medication to risk of developing Reye’s syndrome. The 7 cases were compared with 16 control children who were matched on basis of gender, age, and characteristics of their prodromal illness. Type and quantity of all medications taken by both case and control subjects during the prodromal illness were determined by interviewing parents within 4 weeks after the children were hospitalized. On analysis, the only difference between case and control subjects was in the use of salicylate-containing medications. All of the case subjects used salicylates during their prodromal illness, whereas only half of those in the control group did. Furthermore, the mean salicylate dose in case subjects was almost five times that in the control children. In spite of the limited size of the study, these findings were highly statistically significant.

Although previous authors had noted use of salicylates in association with Reye’s syndrome, Starko’s was the first controlled study to document this putative association. However, the study suffered from several important weaknesses that precluded definitive conclusions. The number of cases was small, there were potential sources of bias such as differential recall of medications or treatment selection based on severity of illness, and control subjects were not proven to have influenza, although their symptom profiles matched those of the case subjects. Nevertheless, when published in 1981, the apparent association of aspirin with risk of Reye’s syndrome caught the attention of the medical community, CDC, US Food and Drug Administration (FDA), and aspirin manufacturers. Starko’s paper was the forerunner of a series of studies to be conducted over the ensuing seven years, all of which essentially confirmed and supported her original findings.

During the 1979 to 1980 season, the Michigan Department of Health conducted a survey of 25 Reye’s syndrome cases and 46 matched control subjects. This survey collected information on 73 potential exposures, including type of residence, medications, type of prodromal illness, dietary history, exposure to toxic substances, and animal exposures. The only significant association found was with salicylate exposure, ie, cases were more likely than were control subjects to have taken salicylates. During the 1980 to 1981 winter, the Michigan investigators focused specifically on medication use. Again, the only difference found was with salicylate use. All 12 cases received salicylate during their prodromal illness, compared with 13 of 29 control subjects, a highly significant difference. These companion studies were published together in June 1982.

During the same period (1978 to 1980), the Ohio Department of Health and the CDC conducted a large case-control study in Ohio to assess the association of infection and medication exposure with risk of Reye’s syndrome. A total of 97 children with Reye’s syndrome were compared with 156 matched control children over a 2-year period. Of the medications taken during the prodromal illness, only salicylate use occurred more frequently in case (97%)}
than in control subjects (71%), again a statistically significant difference. This study was published in August 1982.7

In response to concerns raised by Starko’s study and the yet unpublished Ohio and Michigan studies, the CDC convened an expert panel in October 1981 to review the studies and advise on appropriate action. The FDA also formed a working group in 1981 to analyze and evaluate the available data independently. In addition, the Aspirin Foundation of America, representing major manufacturers and distributors of aspirin products, retained an independent consulting firm, Biometric Research Institute, to conduct a detailed review of the studies.8 It is unlikely that any group of studies before or since has undergone the intense scrutiny to which these studies were subjected. Although the several groups recognized that sources of bias and methodologic errors could possibly explain at least part of the apparent association, a true association between salicylate use and risk of Reye’s syndrome could not be dismissed. Because of this concern, efforts were made during the years 1981 to 1982 to advise health care providers and the public of the possible association and to recommend against use of aspirin in children and adolescents during a viral-like illness.9–12 Nevertheless, the debate raged on, with those challenging the veracity of the studies on one side and those accepting the association of salicylate use with risk of Reye’s syndrome on the other.13,14

In response to the controversy and criticism of the three published studies, a US Public Health Service Task Force was formed to implement an additional study, which was designed to address the issues raised by the various critics. A committee of the Institute of Medicine was appointed to oversee the protocol design and conduct of the study, and to perform scheduled interim review and analysis of the results. A pilot study was conducted from February 1984 through May 1984, primarily to determine feasibility and refine methodology for a larger study. Enrollment was spread across 16 pediatric referral centers in 11 states. Thirty case and 145 control subjects were identified. Although the pilot study was not designed primarily to test the hypothesis of an association between aspirin and Reye’s syndrome, when the Institute of Medicine Committee reviewed the data, the association was so strong that they decided to make the results public. The adjusted odds ratio (OR) for an increased risk for Reye’s syndrome if exposed to aspirin during the prodromal illness was 19, much higher than that in any of the previous studies. This study was published in 1985.15

The main Public Health Service Study was conducted between January 1985 and May 1986 and published in April 1987.16 Enrollment was solicited from 70 pediatric referral centers throughout the United States. Although the largest influenza B epidemic since 1969 occurred in 1985, only 33 cases of Reye’s syndrome were identified, 27 of which were acceptable for analysis. The 27 case subjects were compared with 140 matched control subjects. The original target enrollment was 100 to 200 cases. However, interim analysis showed such a strong statistical association between aspirin use and Reye’s syndrome that the Institute of Medicine advisory committee terminated the study early. The OR for risk of Reye’s syndrome with exposure to aspirin was 40, many times higher than that found in the previous studies! Furthermore, there was evidence of a dose–response effect; eg, not only were cases more likely to have received aspirin, they also took larger doses of aspirin than those control subjects who were given aspirin.

Despite the striking results of the Public Health Service study, concern remained, primarily among the aspirin manufacturers, that the apparent aspirin–Reye’s syndrome association could be primarily attributable to bias in the study design. A study supported by five major aspirin manufacturers was performed from November 1, 1986, through August 24, 1987.17 The study, conducted by investigators at Yale and McGill universities, was designed specifically to eliminate or control for potential sources of bias in its design. By the time this study was initiated, the number of Reye’s syndrome cases had decreased to the extent that enrollment was very slow. Twenty-four case subjects and 48 matched control subjects were eventually enrolled. When analyzed, the OR for developing Reye’s syndrome if exposed to aspirin during a viral prodromal illness was 35, virtually the same as that found in the Public Health Service study. The authors concluded that bias could not explain the association, and this study essentially ended the debate. The second component of this story is presented in the paper by Arrowsmith, and colleagues.4 As early as 1982, initial studies suggesting an association between aspirin use and risk of Reye’s syndrome led to recommendations by news media, private organizations, health departments, and state and federal agencies to avoid use of aspirin in children.9–12 Arrowsmith and colleagues at the FDA analyzed changes in aspirin use and number of cases of Reye’s syndrome reported annually from 1980 to 1985, the period during which information from the studies was being disseminated. Arrowsmith found that physician recommendations to use aspirin for treating children decreased significantly from 1980 through 1985. Likewise, sales of children’s aspirin products fell dramatically during the same period. In contrast, sales of adult aspirin products did not change. The data show that the decline in use of children’s aspirin was apparent as early as 1981, preceding published warnings from the American Academy of Pediatrics and the CDC and several years before the warning in the labeling later required by the FDA. This suggests that publicity arising from Starko’s paper had a significant impact on physician and consumer behavior even before results of the subsequent studies were generally available. Similar changes in aspirin use to treat children were documented in local and regional studies.18–19

Coincident with the decreased use of aspirin, cases of Reye’s syndrome reported annually to the National Reye Syndrome Surveillance System declined from a peak of 658 cases in 1980 to only 93 in 1985 and have declined further during the past decade. The decreased number of cases occurred in view of intensified national surveillance for Reye’s syndrome.
cases, major outbreaks of influenza in 1983, 1984, and 1985, and no change in reported varicella cases during the 6-year period.20,21

Starko’s paper, and those that followed, dramatically and permanently changed the choice of antipyretics for children in North America. Every study supported the relationship between aspirin use and risk of Reye’s syndrome. Furthermore, the ORs increased rather than decreased in the more rigorously designed studies. A formal meta-analysis was not necessary to conclude that this was a real and probably causal association. Fortunately, an acceptable alternative to aspirin that was not associated with increased risk of Reye’s syndrome was readily available. Both the case-control studies and marketing data document the replacement of aspirin with acetaminophen for childhood antipyretic treatment after 1980. Today, acetaminophen products dominate the pediatric antipyretic market, largely because of the documented association of aspirin with increased risk of Reye’s syndrome. The shift from aspirin to acetaminophen in the early 1980s represents a dramatic and rapid change in consumer and physician behavior with respect to antipyretic use in response to public dissemination of information through a variety of media sources. It is worth noting that implementation of public policy on this issue lagged far behind consumer and physician behavior. Nevertheless, careful and rigorous clinical research led to changes in antipyretic use, in spite of economic and political pressures, that reduced dramatically the incidence of a devastating illness for which a specific cause or treatment has not and may never be found.

REFERENCES


COMMENTARY

Apgar Scores as Predictors of Chronic Neurologic Disability, by Karin B. Nelson, MD, and Jonas H. Ellenberg, PhD, Pediatrics, 1981;68:36–44

Comments by Gerald S. Golden, MD

ABSTRACT OF ORIGINAL ARTICLE. Apgar scores were recorded at one and five minutes for ~49,000 infants, and at 10, 15, and 20 minutes for babies who did not achieve a score of 8 or higher at five minutes. These children were followed to 7 years of age. Low Apgar scores were risk factors for cerebral palsy, but 55% of children with later cerebral palsy had Apgar scores of 7 to 10 at one minute, and 73% scored 7 to 10 at five minutes. Of 99 children who had Apgar scores of 0 to 3 at 10, 15, or 20 minutes and survived, 12 (12%) had later cerebral palsy; 11 of the 12 also were mentally retarded (in 10, IQ <50) and half had seizure disorders. Eight children who survived after having very low late Apgar scores and who did not have cerebral palsy had lesser but significant disabilities. Of the children who had Apgar scores of 0 to 3 at 10 minutes or later and survived, 80% were free of major handicap at early school age.

COMMENTARY

The relationship between perinatal asphyxia and prematurity, the condition of the infant at birth, and motor and mental disability has been of interest since 1861 when William John Little,
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Pediatrics 1998;102;259

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://pediatrics.aappublications.org/content/102/Supplement_1/259